No odor of difurylchloroarsine remained. Attempts to steam distil the oil failed, the compound being broken down into furan, arsenious sulfide and arsenic trioxide. The oil was dissolved in ether without further purification, the solution dried and evaporated. On standing the oil turned a light yellow but did not crystallize at the temperature of Dry-Ice; d^{25}_4 1.583.

Anal. Calcd. for $((C_4H_3O)_2As)_2S$: As, 33.30. Found: As, 33.36, 33.44.

2-Chloromercurifuran from Trifurylarsine.—One gram of trifurylarsine was dissolved in 20 cc. of alcohol, a solution of 3.2 g. of mercuric chloride in 100 cc. of water alcohol added, and the solution was heated to boiling and set aside to cool. Well-defined crystals of 2-chloromercurifuran formed and after addition of water to complete the precipitation they were filtered, dried and weighed; yield 1.6 g. or 50%. This material was identified by an analysis for mercury and chlorine and checked against the known compound by a mixed melting point.

Iodination of Trifurylarsine.—One gram of trifurylarsine and 3 g. of iodine were placed in 10 cc. of ether and refluxed for two hours. After evaporating the ether, 20 cc. of water was added. The resulting solution was neutralized with sodium carbonate and the excess iodine removed with sodium thiosulfate. On distillation, 0.6 g. of 2-iodofuran was obtained, 28%. Mercuration of this product gave 5-iodo-2-chloromercurifuran, m. p. 169°.

2,5-Furyldiarsine Tetrachloride.—Sixty grams of 2,5-chloromercurifuran was placed in a 250-cc. flask and 90 g. of arsenic trichloride added, and after standing for three days at room temperature the precipitate of mercuric chloride was filtered out. Removal of excess arsenic trichloride from the filtrate by low pressure distillation left a black viscous material from which nothing organic was distillable at 0.01 mm. Therefore, one-sixth of the filtrate was placed in a 100-cc. flask and 5 g. of iodine in 15 cc. of carbon tetrachloride added. After refluxing for three hours the contents were subjected to steam distillation; yield of 2,5-diodofuran 1.0 g. or 17%.

The production of 2,5-diiodofuran from this arsenical indicates that the original product of arsenation contains the furan nucleus and that the arsenic is in the 2 and 5 positions as expected from the synthesis. However, all products that have been formed at this time by the action of water on this arsenical have only one arsenic atom in the molecule and do not contain the furan nucleus. Their structure will be the subject of further research.

Appreciation is due Dr. Henry Gilman for certain suggestions.

Summary

Some furan arsenicals obtainable from 2-chloromercurifuran have been isolated and described. Evidence has been reported indicating that the carbon–arsenic bond in these arsenicals is cleaved with unusual ease. A furan arsenical has been prepared from 2,5-dichloromercurifuran and its structure determined indirectly. Compounds derivable from this arsenical by the action of water do not contain the furan nucleus.

LINCOLN, NEBRASKA RECEIVED MARCH 18, 1935

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Cinchona Alkaloids in Pneumonia. III. Apocupreines (Apoquinine)

BY C. L. BUTLER AND LEONARD H. CRETCHER

Recent favorable results with ethylapoquinine in the study of experimental and clinical pneumonia[1] have made the chemistry of apoquinine (the alkali-soluble product resulting from the action of demethylating agents on quinine) of great importance. The present paper describes experiments dealing with the preparation of apoquinine which it is believed will be of help in explaining the confusing data in the literature on this subject. Data on the pneumococcicidal action and toxicity of some apoquinine fractions are also presented.

This confusion in the older literature has recently been pointed out by Henry and Solomon[2] and is strikingly shown by the following data on the melting point and specific rotation, respectively, of apoquinine: 160 and −178.1°;[3] 210 and −217°;[4] 160 and −196.4°;[5] 190 and −190.5°;[6] 170 and −216°;[7] 184 and −214°.[2]

Using hydrochloric and sulfuric acids as reagents, we have succeeded in the preparation of apoquinine in two analytically pure forms showing a marked difference in properties. Since a rearrangement, probably of the vinyl group from —CH=CH_2 to =CH—CH_3, invariably accom-

(1) Maclachlan, Permar, Johnston and Kenney, *Am. J. Med. Sci.*, **188**, 699 (1934).

(2) Henry and Solomon, *J. Chem. Soc.*, 1923 (1934).

(3) Hesse, *Ann.*, **205**, 314 (1880).

(4) Lippmann and Fleissner, *Monatsh.*, **16**, 34 (1895); *Ber.*, **28**, 1972 (1895).

(5) Fränkel and Buhlea, *ibid.*, **58**, 559 (1925).

(6) Jarzyński, Ludwiczakówna and Suszko, *Rec. trav. chim.*, **52**, 839 (1933).

(7) Miura and Okamoto, *Jap. J. Med. Sci.*, [1] **5** 1 (1930).

panies or precedes demethylation of quinine, it would appear to be reasonable to assume that the substances isolated are geometric isomers. If this is the case, they bear a relation to cupreine similar to that of the apocinchonines and apocinchonidines[8] to cinchonine and cinchonidine. Because of their closer relationship to cupreine than to quinine, and because the prefix, apo-, has been applied to compounds having similar relationships in the cinchonine series,[8] we shall refer in this paper to apoquinine as crude apocupreine; and to the purified substances isolated from it, as α- and β-apocupreines.

Optical rotational data in the two apocupreine series herein reported are shown in Table I. We can offer no explanation at present for the curious facts that Jarzyński, Ludwiczakówna and Suszko[6] could only isolate the lower rotating β-form; that the earlier experiments in this Laboratory yielded only the higher rotating α-isomer while later ones gave both forms; and that Henry and Solomon[2] apparently were successful in isolating only substances in the higher rotating series. Referring to the older data given above, if the very early preparation of Hesse[3] be disregarded, it is seen that these substances also fall into two definite groups with ranges of specific rotation −215 to −217° and −190 to −196°, very close to those herein reported for α- and β-apocupreines.

The quinine structure is large and complicated and the course of its reactions is readily shifted by comparatively small changes in reaction conditions. Further, there are two main reaction products, α- and β-apocupreines, and both of these may or may not appear in the crude substance. These conditions, together with the additional fact that it is only very recently that crystalline apocupreine salts have been described, account readily for the apparent discrepancies in the apoquinine data in the literature.

TABLE I

SPECIFIC ROTATIONS OF α- AND β-APOCUPREINES AND THEIR SALTS

	α-series	β-series
Bases	−215°	−194°
Monohydrochlorides	−163°	−145°
Dihydrochlorides	−223°	−206°
Acid sulfates	−224°	−208°

It has been stated that apoquinine, although showing a relatively strong pneumococcicidal power *in vitro*, gives practically no protection to mice against pneumococcic infection.[9] No details as to method of preparation of the material used in this research, or as to its purification, are available.[7] In the course of our work, it has been shown that the apocupreine dihydrochlorides have a fairly high pneumococcicidal power *in vitro*, are very low in toxicity toward mice when compared with other members of the cinchona group such as quinine, optochine or ethylapoquinine, and have a protective power similar to that of optochine and ethylapoquinine.

The data shown in Table II are a part of a detailed report on the biological work and on the results of clinical tests using this material, to be presented elsewhere by the medical staff connected with the problem.

Experiments on various alkylated apocupreines are also in progress and will be reported in future papers.

TABLE II

PNEUMOCOCCICIDAL ACTIVITY AND TOXICITY OF APOCUPREINE DIHYDROCHLORIDES TOWARD MICE

	In vitro sterilized in concn. of	Toxicity doses 5 mg.[b] deaths	Protection doses 2 mg.[b] recoveries	
Optochin	1:800,000	25/30	25/30	28/30
α-Apocupreine	1:300,000[a]	0/30	16/20	23/30
β-Apocupreine	Not done	0/30	24/30	

[a] Not tried in higher dilution. [b] Per 20 g. of body weight.

Experimental Part

Specific rotations refer to sodium light; $c = 1$, in water for the salts, in absolute alcohol for the bases; $l = 1$.

The Preparation of α-Apocupreine by the Hydrochloric Acid Method.—Solutions containing 24 g. of dried U. S. P. quinine in 100 cc. of 25% hydrochloric acid were heated in 200-cc. sealed Pyrex tubes for five hours at 142–143°. The resulting solutions were diluted, filtered with Nuchar and worked up as previously described.[5,6] Ten such batches gave 193 g. of crude product. This was converted to dihydrochloride which was then separated by recrystallization from alcohol–ether mixtures into 3 fractions. The first, of 24 g., showed a specific rotation of −175 to 176°; the second, of 68 g., a specific rotation of −219°; the third fraction, of 76 g., was thrown out of solution by ether as an amorphous precipitate with a specific rotation of about −200°. This was further purified by regeneration of the base, conversion into monohydrochloride and two recrystallizations from alcohol; yield, 42 g.; specific rotation, −163°; convertible without loss into the dihydrochloride of specific rotation −219°. It corresponded to 47 g. of this salt. The total yields of crystalline products were thus 24 g. of low rotating salt and 115 g. of high rotating salt.

Further investigation showed both of these fractions to contain non-ionizable halogen. The chlorine content of

(8) Jungfleisch and Léger, *Ann. chim.*, [9] **14**, 59 (1920).

(9) Okamoto and Sogen, *Jap. J. Med. Sci.*, [1] **5**, 4 (1930).

the base from the lower rotating salt was roughly the calculated for an equimolecular mixture of apocupreine and a chlorine derivative of apocupreine such as hydrochloroapocupreine.

Anal. Calcd. for $C_{19}H_{22}O_2N_2$ + $C_{19}H_{23}O_2N_2Cl$: Cl, 5.1. Found: Cl, 6.1.

The base from the higher rotating salt contained about 1% chlorine. Pure chlorine-free α-apocupreine was eventually obtained from this material by extracting with acetone and discarding the acetone insoluble substance, specific rotation −215°. It gave a dihydrochloride of specific rotation −223°.[2]

The Preparation of α- and β-Apocupreines by the Sulfuric Acid Method.—A solution of 50 g. of dried U. S. P. quinine in 200 cc. of 60% sulfuric acid was boiled gently under a reflux condenser for five hours.[5] The crude base was obtained as previously described; yield 37 g.

On attempting to repeat the crystallization of apocupreine monohydrochloride as described by Jarzyński, Ludwiczakówna and Suszko[6] a yield of only 2 g. of salt of specific rotation −145° was obtained. The rest of the material separated repeatedly from water as a gum. However, the crystallization proceeded quite satisfactorily from alcohol as described below.

A solution of 30 g. of dried crude base in 95% alcohol was neutralized with the calculated quantity of aqueous concentrated hydrochloric acid. After evaporation to dryness the salt was ground with a little absolute alcohol, filtered, washed several times with small portions of absolute alcohol and dried; yield, 27 g.; specific rotation −159°. On recrystallization 23 g. of pure α-apocupreine monohydrochloride was obtained; specific rotation −163°.

In many subsequent experiments 100-g. batches of crude apocupreine yielded on one crystallization, monohydrochloride of rotation from −149 to −158°. This material on repeated recrystallization from alcohol yielded 18 g. to 24 g. of β-apocupreine monohydrochloride, specific rotation −145 to −147°; 6 g. to 23 g. of an intermediate fraction, specific rotation −154 to −155°; and 18 g. to 42 g. of α-apocupreine monohydrochloride, specific rotation −163 to −165°.

The bases prepared from α- and β-apocupreine salts had specific rotations −215 and −194°, respectively. Both melted with decomposition at 180 to 190°.

The acid sulfates were prepared by neutralization with the calculated quantity of sulfuric acid and purified by crystallization from alcohol. They had specific rotations of −224 and −208°, for the α- and β-salts, respectively.

Anal. Monohydrochlorides. Calcd. for $C_{19}H_{22}O_2N_2 \cdot HCl$: Cl, 10.2; N, 8.1. Found: Cl, α-salt, 10.2; β-salt, 10.2; intermediate fraction, 10.2. N, α-salt, 7.9; β-salt, 7.8; intermediate fraction 8.0. Dihydrochlorides. Calcd. for $C_{19}H_{22}O_2N_2 \cdot 2HCl$: Cl, 18.5; N, 7.3. Found: Cl, α-salt, 18.3; β-salt, 18.0. N, α-salt, 7.3; β-salt, 7.1. Acid sulfates. Calcd. for $C_{19}H_{22}O_2N_2 \cdot H_2SO_4$: S, 7.85. Found: S, α-salt, 7.8; β-salt, 7.8.

Summary

Evidence has been presented for the existence of apocupreine and its salts in two isomeric forms (possibly geometric). The two bases have been named α- and β-apocupreines. Some properties of these substances have been described.

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[CONTRIBUTION FROM THE SCHOOL OF ENGINEERING RESEARCH, UNIVERSITY OF TORONTO]

Studies of Some Hydrazone and Osazone Reactions

BY E. G. R. ARDAGH AND F. C. RUTHERFORD

Introductory

This research is a continuation, into the field of the sugars, of the investigation of the effect of hydrogen-ion concentration on the rates of formation of phenylhydrazones previously published.[1,2]

The velocity constant, k_1, for the reaction

$$C_6H_5NHNH_2 + C_6H_{12}O_6 \rightleftharpoons C_6H_5NHN{:}C_6H_{12}O_5 + H_2O$$

was determined, polarimetrically, for *d*-glucose, levulose and *d*-galactose under carefully controlled conditions of hydrogen-ion and buffer concentration, using phosphate and acetate buffers.

Experimental

The solutions polarized were made up from solutions of the sugar (Kahlbaum), freshly prepared water-white solutions of pure phenylhydrazine which had been filtered to remove any turbidity, and the indicated buffer solutions made up from stock solutions of either mono-, di- or tri-potassium phosphate with phosphoric acid or potassium acetate with acetic acid. The buffers were prepared from accurately weighed quantities of the salts, and the *p*H of each was determined by means of the quinhydrone electrode to ±0.05 unit. The temperature during each polarization was accurate to ±0.1° as read from a thermometer in the polarimeter tube.

The velocity constants were calculated using the bimolecular formula[3]

$$k_1 t = \frac{2.303}{c} \log \left(\frac{X + c}{X} \right) + C$$

(1) Ardagh and Williams, THIS JOURNAL, **47**, 2976, 2983 (1925).

(2) Ardagh, Kellam, Rutherford and Walstaff, *ibid.*, **54**, 721 (1932).

(3) Conant and Bartlett, *ibid.*, **54**, 2881 (1932).